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(54) Pharmaceutical compositions comprising CS-866 and insulin resistance improving agents and their use for the treatment of arteriosclerosis and xanthoma

PHARMAZEUTISCHE ZUSAMMENSETZUNGEN enthaltend CS-866 und INSULINRESISTENZ VERBESSERNDEM MITTELN und deren Verwendung zur Behandlung von Arteriosklerose und XANTHOM

Compositions pharmaceutiques comprenant CS-866 et des agents reforçants de la resistance a l'insuline et leur utilisation pour le traitement de la sclerose en plaques et du xanthome

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(56) References cited:

EP-A- 0 219 782	**EP-A- 0 332 332**
EP-A- 0 411 395	**EP-A- 0 425 956**
EP-A- 0 603 419	**WO-A-94/19347**
WO-A-95/26188	**US-A- 5 223 522**

- **STRIDES OF MEDICINE, (1995), Vol. 174, No. 10, TORU MURAKAMI, NOBUHIRO YAMADA, "Can ACE Inhibitors Prevent Arteriosclerosis? (in Japanese)", pages 810-813. XP002965198**

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Description

[Technical Field of the Invention]

[0001] The present invention relates to a pharmaceutical composition comprising as its active ingredients an angiotensin II receptor antagonist, namely CS-866, and one or more insulin resistance improving agents selected from the group consisting of troglitazone, pioglitazone and BRL-49653 (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis), and to the use of an angiotensin II receptor antagonist, namely CS-866, and one or more insulin resistance improving agents selected from the group consisting of troglitazone, pioglitazone and BRL-49653 for preparing a pharmaceutical composition (particularly a composition for prevention or treatment of arteriosclerosis).

[Background of the Invention]

[0002] The occurrence of atherosclerosis is increasing with the adoption of Western-style diet and the growth of the aged population. This disease is the main cause of such disorders as myocardial infarction, cerebral infarction and cerebral apoplexy, and there is a need for its effective prevention and treatment. Examples of risk factors which cause atherosclerosis include hyperlipemia (particularly hypercholesterolemia), hypertension and saccharometabolism disorders based on insulin resistance. In addition, there are many cases in which these risk factors occur in the form of complications (Syndrome X), and are considered to be mutually interrelated [Diabetes, 37, 1595-1607 (1988)].

[0003] Efforts have been made for the purpose of preventing and treating atherosclerosis by suppression of various risk factors such as hyperlipemia, hypertension and insulin resistance. Although HMG-CoA reductase inhibitors like pravastatin improve hyperlipemia, their inhibitory activity on arteriosclerosis in a case of administration alone is not enough [Biochim. Biophys. Acta, 960, 294-302 (1988)]. In addition, even insulin resistance improving agents like troglitazone do not exhibit sufficient atherosclerosis inhibitory activity in a case of administration alone (Japanese Patent Application (Kokai) No. Hei 7-41423).

[0004] On the other hand, among drugs for the treatment of hypertension, it has been reported that atherosclerotic lesions are suppressed when angiotensin converting enzyme (ACE) inhibitors that inhibit the renin-angiotensin system [Hypertension, 15, 327-331 (1990)] or angiotensin II receptor antagonists [Jpn. Circ. J., 60 (Suppl. I), 332 (1996)] are administered to animals having normal blood pressure and hypercholesterolemia. Angiotensin II not only exhibits vasoconstrictive activity, but also activity that stimulates the production of growth factors such as PDGF [Hypertension, 13, 706-711 (1989)] and activity that stimulates migration of neutrophils and macrophages [Eur. Heart J., 11, 100-107 (1990)]. Although the mechanism in which renin-angiotensin system inhibitors suppress atherosclerosis is not clear at the present time, there is a possibility that the mechanism for suppressing atherosclerosis may be a function at the site of the lesion which is different from their blood pressure lowering action. However, since inhibitors of renin-angiotensin system are unable to lower serum lipids [J. Cardiovasc. Pharmacol., 15, S65-S72 (1990)], their administration alone has limitations on the treatment of arteriosclerosis.

[0005] In addition, although troglitazone, glibenclamide and captopril are administered concomitantly to diabetes patients, there is no suggestion indicated whatsoever relating to the prevention and treatment of arteriosclerosis [Clin. Pharm., 9 (Supp. 3), 39-60 (1993)].

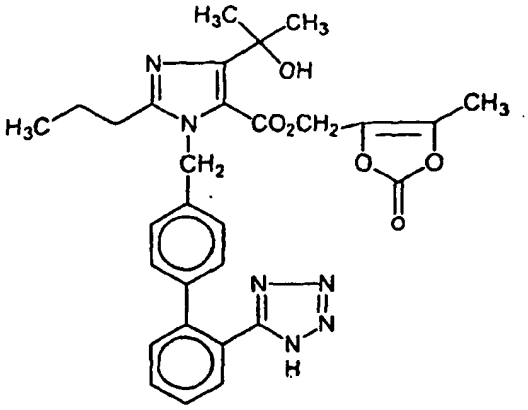
[Disclosure of the Invention]

[0006] As a result of earnestly conducting various research in consideration of the importance of the prevention and treatment of arteriosclerosis, the inventors of the present invention found a method to solve the above-mentioned problems involved in the prior art and to obtain a preventive and/or therapeutic effect on arteriosclerosis by using the combination of CS-866, and of one or more drugs selected from the group consisting of troglitazone, pioglitazone, and BR-49653.

[0007] The present invention provides a pharmaceutical composition as defined in Claim 1; a kit as defined in Claim 9, and uses as defined in Claim 16 and Claim 23.

[0008] Preferred embodiments of the invention are defined in the dependent claims.

[0009] The active ingredients of the pharmaceutical composition of the present invention (particularly a pharmaceutical composition for the prevention or treatment of arteriosclerosis) include CS-866, and one or more drugs selected from the group consisting of troglitazone, pioglitazone and BRL-49653.



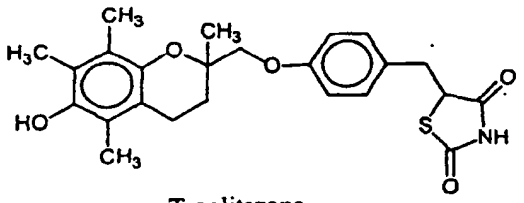
CS-866

[0010] CS-866 has the structural formula shown above, and is described in Japanese Patent Application No. (Kokai) No. Hei 5-78328 and the like, and its chemical name is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazole-5-carboxylate. The CS-866 of the present application includes its carboxylic acid derivative, pharmacologically, acceptable esters of its carboxylic acid derivative (such as CS-866) and their pharmacologically acceptable salts.

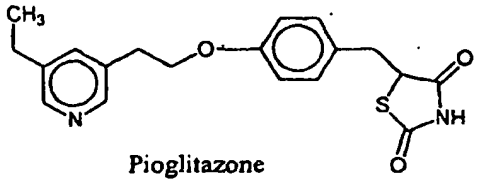
[0011] In addition, hydrates of the above-mentioned compounds are also included in the present invention.

[0012] The insulin resistance improving agents as another active ingredient of the present invention are troglitazone, pioglitazone, or BRL-49653, preferably troglitazone or pioglitazone, and most preferably troglitazone.

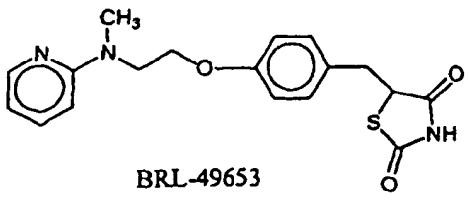
[0013] The following indicates the chemical planar structural formulae of the insulin resistance improving agents used according to the present invention.



Troglitazone



Pioglitazone



BRL-49653

[0014] Troglitazone is described in Japanese Patent Application (Kokai) No. Sho 60-51189, U.S. Patent No. 4,572,912 and the like, and its chemical name is 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-thiazolidinedione. The troglitazone of the present application includes its pharmacologically acceptable salts.

[0015] Pioglitazone is described in Japanese Patent Application (Kokai) No. Sho 55-22636, U.S. Patent No. 4,287,200 and the like, and its chemical name is 5-[4-[2-(5-ethyl-pyridin-2-yl)ethoxy]phenylmethyl]-2,4-thiazolidinedione. The pioglitazone of the present application includes its pharmacologically acceptable salts.

[0016] BRL-49653 is described in Japanese Patent Application (Kokai) No. Hei 1-131169, U.S. Patent No. 5,002,953 and the like, and its chemical name is 5-[4-[2-[N-methyl-N-(pyridin-2-yl)amino]ethoxy]phenylmethyl]-2,4-thiazolidinedione. The BRL-49653 of the present application includes its pharmacologically acceptable salts.

[0017] Where the above-mentioned insulin resistance improving agents of the present invention have asymmetric carbons, said resistance improving agents the present, invention also include their optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included in the present invention.

[0018] Preferable examples of the pharmaceutical composition of the present invention are as follows:

(1) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone and pioglitazone; and,

(2) a pharmaceutical composition wherein as an active ingredient, the insulin resistance improving agent is troglitazone.

[Effect of the Invention]

[0019] The active ingredients of the pharmaceutical composition of the present invention (particularly a composition for prevention or treatment of arteriosclerosis), have excellent inhibitory action on aortosclerosis and excellent inhibitory action against onset of xanthoma occurring in limb joints, and low toxicity. Consequently, they are useful as drugs for the prevention and treatment (particularly for treatment) of arteriosclerosis or xanthoma.

[0020] According to the present invention, the combinations according to the invention exhibit excellent effects by using two of these agents in combination as compared with being used alone. In addition, these effects can be achieved without requiring that both types of agents be present in the body simultaneously.

[0021] Namely, such effects can be obtained even if both types of agents do not simultaneously have certain concentrations in the blood. According to hypothesis, if two types of agents used in the present invention are both incorporated in vivo and reach the receptors, they have the effect of turning on a switch in vivo. Thus, even if it appears that such effects are not demonstrated at their blood concentrations in course of time after their administration, the switch is actually still on, thereby allowing demonstration of preventive or therapeutic effects on arterial sclerosis possessed by the one type of substance. When the other type of agent is administered in this state, in addition to the preventive or therapeutic effects on arterial sclerosis possessed by that agent, the effects of the drug initially administered are combined to obtain excellent effects. Naturally, since it is convenient clinically to administer two types of agents simultaneously, the combinations according to the present invention can be administered in the form of a combination drug. In cases where it is undesirable to physically mix both agents simultaneously in consideration of pharmaceutical formulation technology, each individual agent may be administered simultaneously. In addition, as was stated above, since excellent effects are demonstrated even if the two types of agents are not administered simultaneously, each individual agent can also be administered at a suitable interval in succession. The maximum administration interval of the two types of agents to demonstrate the excellent effects brought about by said two types of agents can be determined by clinical or animal studies.

[Industrial Applicability]

[0022] The administration route of the drugs used in the present invention is typically the oral administration route. Thus, the two types of agents can either be prepared in the form of two separate administrations or in the form of a single administration by physically mixing the two types of agents. The administration form can be, for example, a powder, granules, tablet or capsule and the like, and can be prepared by using conventional pharmaceutical formulation techniques.

[0023] The dose and administration ratio of the drugs used in the present invention can be changed over a wide range according to various conditions such as the individual activity of each agent, the patient's symptoms, age and body weight, and the like. For example, in the case of insulin resistance improving agents, since the in vivo activities of troglitazone and BRL-49653 by using a diabetic animal model are different, the dose of these two agents may be different by a factor of ten or more. In addition, for both CS-866 and insulin resistance improving agents, their doses in the case used for prevention or treatment of arteriosclerosis in the present invention can be lower than their dose for use as hypotensive agents and diabetes therapeutic agents respectively, which are their well-known applications. In addition, their doses can be made even lower due to the excellent effects resulting from combined use of both types of agents. For example, in the case of using CS-866 and troglitazone for the object of the present invention, their doses are lower than the approximately 5 to 100 mg and approximately 10 to 2000 mg, respectively, which are the doses for

adults (mg/day) for use as a hypotensive agent and diabetes therapeutic agent in their well-known applications, being able to be approximately 1 to 80 mg and approximately 1 to 1000 mg, respectively.

[0024] As has been described above, the doses of the drugs consisting of CS-866 and of the insulin resistance improving agents can be varied over a wide range, in general, and their doses for adults (mg/day) are approximately 0.5 to 100 mg and approximately 0.05 to 1,500 mg, respectively.

[0025] The ratio of the doses of these two types of agents can also be varied over a wide range, in general, and the dose ratio of the CS-866 to the insulin resistance improving agents can be, in terms of weight ratio, within the range from 1:200 to 200:1.

[0026] In the present invention, the drugs consisting of CS-866 and the insulin resistance improving agents are administered at the respective doses described above once a day or divided among several times per day, and may be administered simultaneously or separately at respectively different times.

[Best Mode for Carrying Out the Invention]

[0027] The present invention will be described more specifically by way of Examples and Preparation examples.

(Example 1)

Arterial sclerosis Progress Inhibitory Effect

[0028] A certain amount of an agent was administered orally for 32 weeks to 2-3 months old WHHL rabbits [Watanabe genetically hyperlipemic rabbits: supra (Biochimica et Biophysica Acta), etc.] in groups of 4 to 7 animals each. Incidentally, food consumption was restricted to 120 g/day per animal. Blood samples were collected immediately before administration of the agent and 4, 8, 12, 16, 20, 24, 28 and 32 weeks after the start of administration to measure total cholesterol levels (mg/dl). There were no changes observed in any of the dose groups as compared with the control group to which no agents were administered. The test animals were subjected to autopsy in the 32nd week to investigate the surface area of aortic lesions (%) and the incidence of xanthoma in finger joints (%). Those results are shown in Tables 1 and 2.

[Table 1]

Surface Area of Aortic Lesions							
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Lesion surface area (%)			
				Arcuate region	Thoracic part	Abdominal region	Overall
1	CS-866 + Troglitazone	1 + 25	5	52±10	9±3	13±2	21±4
	CS-866	1	6	68±10	26±8	19±5	34±7
	Troglitazone	25	7	80±7	57±12	32±8	54±9
	Control	-	7	83±6	59±7	39±4	56±4

[Table 2]

Incidence of Xanthochromia in Finger Joints						
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Xanthochromia incidence (%)		
				Fore-limbs	Hind-limbs	Overall
1	CS-866 + Troglitazone	1 + 25	4	75	63	69

[Table 2] (continued)

Incidence of Xanthochromia in Finger Joints						
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Xanthochromia incidence (%)		
				Fore-limbs	Hind-limbs	Overall
	CS-866	1	6	100	100	100
	Troglitazone	25	7	93	86	89
	Control	-	7	100	100	100

(Example 2)

Arterial sclerosis Progress Inhibitory Effect

[0029] A certain amount of an agent was administered orally for 31 weeks to 2-3 months old WHHL rabbits [Watanabe genetically hyperlipemic rabbits: described supra (Biochimica et Biophysica Acta), etc.] in groups of 5 to 7 animals each. Incidentally, food consumption was restricted to 100 g/day per animal. Blood samples were collected immediately before administration of the agent and 8, 16, 24 and 31 weeks after the start of administration to measure total cholesterol levels (mg/dl). There were no changes observed in any of the dose groups as compared with the control group to which no agents were administered. In addition, the test animals were subjected to autopsy in the 31st week to investigate the surface area of aortic lesions (%) and the incidence of xanthoma in finger joints. Those results are shown in Table 3.

[Table 3]

Surface Area of Aortic Lesions							
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Lesion surface area (%)			
				Arcuate region	Thoracic part	Abdominal region	Overall
2	CS-866 + pioglitazone	0.5 + 20	6	62±8	29±10	24±6	36±7
3	CS-866 + BRL-49653	0.5 + 2.5	5	52±5	32±7	25±5	34±5
	CS-866	0.5	7	66±5	41±10	32±8	44±7
	Pioglitazone	20	7	65±6	62±12	32±6	52±8
	BRL-49653	2.5	6	83±2	54±12	29±4	52±5
	Control	-	7	84±5	59±9	32±11	54±8

(Formulation Example 1)	
Tablets	
CS-866	4.0 mg
Troglitazone	100.0
Lactose	244.0
Cornstarch	50.0
Magnesium stearate	400 mg

[0030] The above-mentioned prescriptions are mixed and formed into tablets with a tablet-making machine to obtain tablets containing 400 mg per tablet.

[0031] These tablets can be provided with a sugar-coating if necessary.

Claims

1. A pharmaceutical composition comprising as its active ingredients CS-866 and one or more drugs selected from the group consisting of troglitazone, pioglitazone and BRL-49653.

2. A pharmaceutical composition according to claim 1, comprising CS-866 and one or more drugs selected from the group consisting of troglitazone and pioglitazone.

3. A pharmaceutical composition according to claim 2, comprising CS-866 and troglitazone.

4. A pharmaceutical composition according to any one of claims 1 to 3, for the treatment or prevention of arteriosclerosis or xanthoma.

5. A pharmaceutical composition according to any one of claims 1 to 3, for the treatment or prevention of arteriosclerosis.

6. A pharmaceutical composition according to any one of claims 1 to 3, for the treatment of arteriosclerosis.

7. A pharmaceutical composition according to any one of claims 1 to 3, for the treatment or prevention of xanthoma.

8. A pharmaceutical composition according to any one of claims 1 to 3, for the treatment of xanthoma.

9. A kit including a plurality of containers in which at least one of said containers contains CS-866 and at least one different container contains one or more drugs selected from the group consisting of troglitazone, pioglitazone and BRL-49653, for the treatment or prevention of arteriosclerosis or xanthoma.

10. A kit according to claim 9, wherein said at least one different container contains one or more drugs selected from the group consisting of troglitazone and pioglitazone.

11. A kit according to claim 10, wherein said at least one different container contains troglitazone.

12. A kit according to any one of claims 9 to 11, for the treatment or prevention of arteriosclerosis.

13. A kit according to any one of claims 9 to 11, for the treatment of arteriosclerosis.

14. A kit according to any one of claims 9 to 11, for the treatment or prevention of xanthoma.

15. A kit according to any one of claims 9 to 11, for the treatment of xanthoma.

16. The use of one or more drugs selected from troglitazone, pioglitazone and BRL-49653 in the preparation of a medicament for use, in combination with CS-866, in the treatment or prevention of arteriosclerosis or xanthoma.

17. The use according to claim 16 of one or more drugs selected from troglitazone and pioglitazone in the preparation of a medicament for use, in combination with CS-866, in the treatment or prevention of arteriosclerosis or xanthoma.

18. The use according to claim 17 of troglitazone in the preparation of,a medicament for use, in combination with CS-866, in the treatment or prevention of arteriosclerosis or xanthoma.

19. The use according to any one of claims 16 to 18, in the treatment or prevention of arteriosclerosis.

20. The use according to any one of claims 16 to 18, in the treatment of arteriosclerosis.

21. The use according to any one of claims 16 to 18, in the treatment or prevention of xanthoma.

22. The use according to any one of claims 16 to 18, in the treatment of xanthoma.

23. The use of a composition as defined in any ones of claims 1 to 3 in the preparation of a medicament for use in the treatment or prevention of arteriosclerosis or xanthoma.

24. The use according to claim 23, in the treatment or prevention of arteriosclerosis.

25. The use according to claim 23, in the treatment of arteriosclerosis.

26. The use according to claim 23, in the treatment or prevention of xanthoma.

27. The use according to claim 23, in the treatment of xanthoma.

Patentansprüche

1. Arzneimittelzusammensetzung, die als aktiven Bestandteil CS-866 und ein oder mehrere Arzneimittel enthält, die aus der aus Troglitazone, Pioglitazone und BRL-49653 bestehenden Gruppe ausgewählt sind.

2. Arzneimittelzusammensetzung nach Anspruch 1, die CS-866 und ein oder mehrere Arzneimittel enthält, die aus der aus Troglitazone und Pioglitazone bestehenden Gruppe ausgewählt sind.

3. Arzneimittelzusammensetzung nach Anspruch 2, die CS-866 und Troglitazone enthält.

4. Arzneimittelzusammensetzung nach einem der Ansprüche 1 bis 3 für die Behandlung oder die Verhinderung von Arteriosklerose oder Xanthoma.

5. Arzneimittelzusammensetzung nach einem der Ansprüche 1 bis 3 zur Behandlung oder Verhinderung von Arteriosklerose.

6. Arzneimittelzusammensetzung nach einem der Ansprüche 1 bis 3 zur Behandlung von Arteriosklerose.

7. Arzneimittelzusammensetzung nach einem der Ansprüche 1 bis 3 zur Behandlung oder Verhinderung von Xanthoma.

8. Arzneimittelzusammensetzung nach einem der Ansprüche 1 bis 3 zur Behandlung von Xanthoma.

9. Kit, der mehrere Behälter umfasst, wobei mindestens einer der Behälter CS-866 enthält und mindestens ein anderer Behälter ein oder mehrere Arzneimittel enthält, die aus der aus Troglitazone, Pioglitazone und BRL-49653 bestehenden Gruppe ausgewählt sind, zur Behandlung oder Verhinderung von Arteriosklerose oder Xanthoma.

10. Kit nach Anspruch 9, wobei der mindestens eine andere Behälter ein oder mehrere Arzneimittel enthält, die aus der aus Troglitazone und Pioglitazone bestehenden Gruppe ausgewählt sind.

11. Kit nach Anspruch 10, worin der mindestens eine andere Behälter Troglitazone enthält.

12. Kit nach einem der Ansprüche 9 bis 11 zur Behandlung oder Verhinderung von Arteriosklerose.

13. Kit nach einem der Ansprüche 9 bis 11 zur Behandlung von Arteriosklerose.

14. Kit nach einem der Ansprüche 9 bis 11 zur Behandlung oder Verhinderung von Xanthoma.

15. Kit nach einem der Ansprüche 9 bis 11 zur Behandlung von Xanthoma.

16. Verwendung eines oder mehrerer Arzneimittel, die unter Troglitazone, Pioglitazone und BRL-49653 ausgewählt sind, zur Herstellung eines Arzneimittels für die kombinatorische Verwendung mit CS-866 in der Behandlung oder Verhinderung von Arteriosklerose oder Xanthoma.

17. Verwendung nach Anspruch 16 von einem oder mehreren Arzneimitteln, die unter Troglitazone und Pioglitazone ausgewählt sind, zur Herstellung eines Arzneimittels für die kombinatorische Verwendung mit CS-866 in der Behandlung oder Verhinderung von Arteriosklerose oder Xanthoma.

18. Verwendung nach Anspruch 17 von Troglitazone zur Herstellung eines Arzneimittels für die kombinatorische Verwendung mit CS-866 in der Behandlung oder Verhinderung von Arteriosklerose oder Xanthoma.

19. Verwendung nach einem der Ansprüche 16 bis 18 in der Behandlung oder Verhinderung von Arteriosklerose.

20. Verwendung nach einem der Ansprüche 16 bis 18 in der Behandlung von Arteriosklerose.

21. Verwendung nach einem der Ansprüche 16 bis 18 in der Behandlung oder Verhinderung von Xanthoma.

22. Verwendung nach einem der Ansprüche 16 bis 18 in der Behandlung von Xanthoma.

23. Verwendung einer Zusammensetzung nach einem der Ansprüche 1 bis 3 zur Herstellung eines Arzneimittels für die Verwendung in der Behandlung oder Verhinderung von Arteriosklerose oder Xanthoma.

24. Verwendung nach Anspruch 23 in der Behandlung oder Verhinderung von Arteriosklerose.

25. Verwendung nach Anspruch 23 in der Behandlung von Arteriosklerose.

26. Verwendung nach Anspruch 23 in der Behandlung oder Verhinderung von Xanthoma.

27. Verwendung nach Anspruch 23 in der Behandlung von Xanthoma.

Revendications

1. Composition pharmaceutique comprenant comme composants actifs le CS-866 et un ou plusieurs médicaments sélectionnés dans le groupe constitué de la troglitazone, la pioglitazone et le BRL-49653.

2. Composition pharmaceutique selon la revendication 1, comprenant le CS-866 et ou plusieurs médicaments sélectionnés dans le groupe constitué de la troglitazone et la pioglitazone.

3. Composition pharmaceutique selon la revendication 2, comprenant le CS-866 et la troglitazone.

4. Composition pharmaceutique selon l'une quelconque des revendications 1 à 3, pour le traitement ou la prévention de l'artériosclérose ou du xanthome.

5. Composition pharmaceutique selon l'une quelconque des revendications 1 à 3, pour le traitement ou la prévention de l'artériosclérose.

6. Composition pharmaceutique selon l'une quelconque des revendications 1 à 3, pour le traitement de l'artériosclérose.

7. Composition pharmaceutique selon l'une quelconque des revendications 1 à 3, pour le traitement ou la prévention du xanthome.

8. Composition pharmaceutique selon l'une quelconque des revendications 1 à 3, pour le traitement du xanthome.

9. Kit incluant plusieurs conteneurs dans lesquels au moins un desdits conteneurs contient le CS-866 et au moins un conteneur différent contient un ou plusieurs médicaments sélectionné dans le groupe constitué de la troglitazone, la pioglitazone et le BRL-49653, pour le traitement ou la prévention de l'artériosclérose ou du xanthome.

10. Kit selon la revendication 9, dans lequel ledit au moins un conteneur différent contient un ou plusieurs médicaments sélectionnés dans le groupe constitué de la troglitazone et la pioglitazone.

11. Kit selon la revendication 10, dans lequel ledit au moins un conteneur différent contient la troglitazone.

12. Kit selon l'une quelconque des revendications 9 à 11, pour le traitement ou la prévention de l'artériosclérose.

13. Kit selon l'une quelconque des revendications 9 à 11, pour le traitement ou la prévention du xanthome.

14. Kit selon l'une quelconque des revendications 9 à 11, pour le traitement de l'artériosclérose.

15. Kit selon l'une quelconque des revendications 9 à 11, pour le traitement du xanthome.

16. Utilisation d'un ou plusieurs médicaments sélectionnés parmi la troglitazone, la pioglitazone, et le BRL-49653 pour la préparation d'un médicament destiné à être utilisé, en combinaison avec le CS-866, pour le traitement et la prévention de l'artériosclérose ou du xanthome.

17. Utilisation selon la revendication 16 d'un ou plusieurs médicaments sélectionnés parmi la troglitazone et la pioglitazone, pour la préparation d'un médicament destiné à être utilisé, en combinaison avec le CS-866, pour le traitement ou à la prévention de l'artériosclérose ou du xanthome.

18. Utilisation selon la revendication 17 de la troglitazone pour la préparation d'un médicament destiné à être utilisé, en combinaison avec le CS-866, pour le traitement ou la prévention de l'artériosclérose ou du xanthome.

19. Utilisation selon l'une quelconque des revendications 16 à 18, pour le traitement ou la prévention de l'artériosclérose.

20. Utilisation selon l'une quelconque des revendications 16 à 18, pour le traitement de l'artériosclérose.

21. Utilisation selon l'une quelconque des revendications 16 à 18, pour le traitement ou la prévention du xanthome.

22. Utilisation selon l'une quelconque des revendications 16 à 18, pour le traitement du xanthome.

23. Utilisation d'une composition telle que définie dans l'une quelconque des revendications 1 à 3 pour la préparation d'un médicament destiné à être utilisé pour le traitement ou la prévention de l'artériosclérose ou du xanthome.

24. Utilisation selon la revendication 23, pour le traitement ou la prévention de l'artériosclérose.

25. Utilisation selon la revendication 23, pour le traitement de l'artériosclérose.

26. Utilisation selon la revendication 23, pour le traitement ou la prévention du xanthome.

27. Utilisation selon la revendication 23, pour le traitement du xanthome.